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APPLICATION NUMBER	FILING DATE	GNER	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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18M1/0805

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EXAMINER	
GAMBEL, P	
ART UNIT	PAPER NUMBER
1806	6

DATE MAILED: 08/05/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 6/16/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-22 is/are pending in the application.
Of the above, claim(s) 2,4,7,8,11,19-22 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1,3,5,6,9,10,12-18 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892 ☑ NOTICE TO COMPLY S&R RULES
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's election of Group I and the species an unmodified endothelial cells (B) and enhancing angiogenesis (A) in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

Claims 1, 3, 5, 6, 9, 10 and 12-18 are being acted upon as the elected invention.

Claims 2, 4, 7, 8, 11, 19-22 have been withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected inventions.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825 (see the specification at page 10, line 22). However, this application fails to comply with the requirements set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is required to fulfill these requirements.

3. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

Under 37 CFR 1.84(b), the applicant must file a petition with fee requesting acceptance of the color and black and white photographs. The petition is decided in the Office of the Group Director.

It is anticipated that such a petition will be granted only when the PTO has determined that a color photograph is the only practical medium by which to disclose in a printed utility patent, the subject matter to be patented.

The petition must also be accompanied by a proposed amendment to insert the following language as the first paragraph in the portion of the specification containing a Brief Description of the Drawings:

The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The specification is objected to and claims 1, 3, 5, 6, 9, 10 and 12-18 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

There is a lack of predictability that the skilled artisan can administer an effective amount of endothelial progenitor cells, as the resident population of endothelial cells is competent to respond to administered angiogenic cytokines (Asahara et al., Science, 1997).

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective neovascularization with endothelial cells, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for enhancing angiogenesis.

7. Claims 1, 3, 5, 6, 9, 10 and 12-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for endothelial progenitor cells that are $CD34^+$, $flk\text{-}1^+$, $tie\text{-}2^+$ does not reasonably provide enablement for any endothelial progenitor cell. There is insufficient direction and guidance as to the identification of any other type of endothelial progenitor cell that may result in neovascularization The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

8. Claims 1, 3, 5, 6, 9, 10 and 12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, 5, 6, 9, 10 and 12 are indefinite and ambiguous in the recitation of "regulating angiogenesis" ... "determining the change in angiogenesis necessary" ... "an effective amount" ... "to accomplish the desired result" because it is unclear what is the nature of the regulation, what changes are being determined, what constitutes the effective amount and the desired result.

Applicant is reminded not to add any new matter.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

11. Claims 1 and 3 are rejected under 35 U.S.C. § 102(a) as being anticipated by Asahara et al. (Circulation 1996). Asahara et al. teach identifying endothelial progenitor cells and their administration to induce angiogenesis in ischemic tissues (see Abstract). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods.

12. Claims 1 and 3 are rejected under 35 U.S.C. § 102(a) as being anticipated by Noishiki et al. (Nature Medicine, 1996). Nosishiki et al. teach transplanting bone marrow cells resulting in the inducement of capillary growth (see entire document). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods.

13. Claims 1, 3, 5, 6, 9, 10 and 12-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Asahara et al. (Circulation 1996) OR Noishiki et al. (Nature Medicine, 1996) in view of Shi et al. (J. Vasc. Surg. 1994), Bikfalvi et al. (Leukemia, 1994) and Asahara et al. (Circulation, 1995). The instant claims are drawn to methods of enhancing angiogenesis or blood cell formation with endothelial cells or endothelial progenitor cells.

Asahara et al. (Circulation 1996) identifying endothelial progenitor cells and their administration to induce angiogenesis in ischemic tissues (see Abstract). Asahara et al. differs from the instant methods by not teaching the use of additional cytokines, treating the breadth of clinical conditions, and using the progenitor cells isolated from the same individual per se.

Noishiki et al. teach transplanting bone marrow cells resulting in the inducement of capillary growth (see entire document). This reference teaches that the bone marrow has stem cells but does teach isolating endothelial progenitor cells themselves. The reference does not teach using exogenous cytokines per se, but does teach cytokines such as FGF as well as products from other cell types are important for endothelial growth.

Shi et al. teaches the proof of fallout endothelialization from grafts which relies upon progenitor cells from the circulation and the applicability of this for endothelialization including angioplasty (see entire document).

Bikfalvi et al. and Asahara et al. teach the importance of various angiogenic factors including their combination on angiogenesis in vivo, which was important for revascularization therapeutic strategies (see entire documents).

Given the knowledge that stem or progenitor cells were in the bone marrow and in the blood, the ordinary artisan would have isolated marrow or blood from the patient of interest to obtain endothelial progenitor cells and reintroduce such cells into said patients upon their need. In the absence of any claimed properties or limitations of the endothelial progenitor cells, these claims read on bone marrow or blood cells themselves, as such tissues were known and taught to comprise endothelial progenitor cells, as taught by Noishiki et al. and Shi et al. Asahara et al. teaches the claimed endothelial progenitor cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to select endothelial progenitor cells as a therapeutic regimen to induce neovascularization in patients of need. It was known at the time the invention was made that the targeted patients were patients in need of therapeutic regimens that resulted in neovascularization. It was known at the time the invention was made that autologous transplantation was important to avoid transplant rejection, as was well practiced in bone marrow transplantation at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
August 4, 1997

Application No. 08/744882

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☑ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☑ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☑ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.

Application No: 08/744382

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☑ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

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Other: _____

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☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

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